DEPARTMENT OF HEALTH & HUMAN SERVICES PUBLIC HEALTH SERVICE
Food and Drug Administration

Memorandum

Center for Biologics Evaluation and Research
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Division of Clinical Trial Design and Analysis
HFM-576

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From: M.Walton, DCTDA

Subject: Data Overview and Regulatory Recommendation
BLA STN 103979 / 0
Genzyme: Aglasidase beta for Fabry Disease

To: BLA file

Background

This document includes an overview of the data submitted to FDA by Genzyme in support of their BLA to market agalsidase beta for treatment of Fabry disease, FDA assessment of the data and regulatory circumstances, and recommendation for approval. Only a very brief review of the clinical data is included in this document; for a complete review of the data the two documents by Dr. J. Kaiser should be consulted.

Genzyme conducted clinical development of agalsidase beta under IND and submitted a BLA in June 2000. The initial submission to this BLA contained data from three clinical trials; an open label phase 1 study, a randomized placebo-controlled study (AGAL-002) which focused upon a histologic evaluation of renal biopsies as an endpoint, and 6 months of an open label treatment follow-on study (AGAL-005) for patients who had participated in AGAL-002. Genzyme requested marketing under the Accelerated Approval regulations based on these data.

Evidence of Effect

As described by Dr. Kaiser, these studies have shown a striking effect upon the accumulation of the enzyme substrate within certain cells, particularly capillary endothelium. The initial data submitted to the agency left uncertain the breadth or durability of this effect. Following FDA requests to Genzyme, additional data were submitted which demonstrated that while not all cell types show a marked decrease in substrate accumulation (e.g. renal podocytes, with a limited degree of reduction in substrate accumulation) there are a variety of cell types with moderate and several that show marked reduction in substrate accumulation.

Antibody formation is widespread in these patients after receiving multiple infusions of the enzyme. Some patients have worsening infusions reactions associated with antibodies. There is potential that some subjects will have loss of effect as antibodies theoretically may either neutralize the enzyme or alter the cellular distribution or extent of enzyme uptake. FDA requested further information from Genzyme to better assess these concerns. With the larger experience submitted to FDA in the later Genzyme BLA responses it is apparent that the infusion reactions are largely amenable to medical management without discontinuation of the infusions. The longer duration data submitted in response to these requests have indicated that antibodies are highly persistent and widespread. Nonetheless, the pharmacodynamic effect of near-absent deposition of substrate in capillary endothelium persisted despite antibodies, and have continued to persist to 2- ½ years in patients evaluated at the longer durations.

Accelerated Approval and Substrate Accumulation

The study submitted by Genzyme is an adequate and well-controlled clinical trial which demonstrated an effect of agalsidase beta on substrate accumulation within certain cell types. Substrate accumulation within capillary endothelial cells is not a disease feature that is directly and immediately consciously sensed by patients, nor is it a disease feature routinely assessed by physicians and validated for a relationship to clinically discernable consequences. Thus, cellular substrate accumulation does not constitute a clinically meaningful endpoint, and effects on intracellular substrate accumulation should not be regarded as substantial evidence of clinical efficacy.

While Genzyme's study did assess clinically meaningful endpoints, no effect on these were demonstrated. A variety of reasons may explain why no effect was observed, but chief among them may be that the study was not designed with the intent to demonstrate clinical efficacy. The study was relatively short for a disorder where progression to renal failure may take many years. Although small, AGAL-002 was nonetheless the largest study conducted in this small disease-population to that time. It is also unknown which phase of the disease may be most amenable to demonstrating a clinical impact of treatment; so it is unknown if the most sensitive portion of the disease population was being studied in AGAL-002. Therefore, the clinical efficacy data that was obtained can be interpreted as neither evidence in favor nor against agalsidase beta treatment leading to clinical benefit.

However, Genzyme has requested to market agalsidase beta under the Accelerated Approval framework. The specific aspect proposed by Genzyme is for marketing on the basis of a surrogate endpoint (21CFR601.41). Genzyme has proposed that the effect demonstrated is a suitable surrogate endpoint basis for marketing under Accelerated Approval.

The Accelerated Approval regulations provide that FDA may grant marketing approval on the basis of adequate and well-controlled clinical trials establishing that the product has an effect upon a surrogate endpoint that is reasonably likely to predict clinical benefit. Approval under these regulations requires that the applicant study the product further to verify and describe the clinical benefit. The regulation states the expectation that the verification study, if a postmarketing study,

would usually be underway at the time of the approval, and that the verification study should also be adequate and well-controlled.

The underlying basis of Fabry disease is well understood; it is an X-linked enzyme deficiency leading to a lipid storage disorder. Lipid storage occurs in a wide variety of cell types, and consequently there are a wide variety of signs and symptoms from different organ systems. Among the most prominent are pain due to peripheral nerve injury, progressive renal impairment leading to renal failure, cardiac impairment leading to both mechanical and rhythm dysfunction and stroke. The exact mechanism leading to the pathologic physiology is not as well defined as the primary enzyme defect. However, the there is wide spread belief that a number of the organ injury manifestations are related to vascular injury. It is believed that while this may not be the sole pathologic process, progressive substrate accumulation within vascular walls will ultimately lead to local vessel occlusion, with organ impairment as a consequence.

Agalsidase beta is a recombinant form of the defective enzyme. Genzyme has proposed that by reducing the substrate accumulation to near-normal (i.e., no apparent substrate accumulation) levels in capillary endothelium, an impact on the vascular-related organ injury can be predicted. Chief among these benefits would be delay the development of renal failure. FDA has reviewed the propositions put forth by Genzyme, and has additionally received discussion of this matter at a public Advisory Committee in January 2003.

Vascular injury does appear to be an important mechanism of promoting the progressive organ impairment, and substrate accumulation within vascular walls is the basis for this. The exact (quantitative) relationship between the amount of substrate accumulation and the degree or rate of vascular ischemia is unknown and not addressed in any information submitted by Genzyme. It is unknown if reducing substrate accumulation by half might slow vascular injury by half, or if there is a threshold effect, wherein some specific amount of accumulation will invariably lead to vascular occlusion and thus no change in the clinical expression of the disease. However, by focusing upon a near-elimination of all accumulation within a specific cell type Genzyme's data appear to overcome these concerns. Genzyme has shown that capillary endothelium are altered by the enzyme treatment to achieve a near-normal appearance with regard to accumulation. Vessels (capillaries in this case) that are essentially near-normal in appearance may well lead to an altered development of vascular occlusion, and thus to an alteration in expression of the clinical impairments of the disease. The Advisory Committee has also supported this assessment of the potential impact of near-absence of capillary accumulation, as well as concurring that the evidence submitted by Genzyme have demonstrated this effect on capillary endothelium.

Consequently, FDA has determined that Genzyme has shown an effect upon a surrogate endpoint reasonably likely to predict a clinical benefit.

Continued Evaluation to Verify the Clinical Benefit

Genzyme has been fully aware of FDA's concern with addressing the need for directly assessing the clinical benefit associated with use of the product, and thus has also undertaken to address the requirement for a clinical benefit verification study. In early 2001 Genzyme finalized design and

initiated a randomized, placebo controlled clinical study (AGAL-008) examining the effect of agalsidase beta on a composite endpoint of renal, cardiac or cerebrovascular disease progression events. The majority of the study enrollment was completed by the fall of 2002, although Genzyme continued to enroll into the study, and final enrollment exceeded the number planned as needed to ensure adequate statistical powering. According to the study design, it is expected that all necessary data collection will be completed in approximately January 2004. Continuation of this study to completion will be a post marketing commitment (PMC) from Genzyme.

However, there is thought to be a high potential for drop-out of patients (especially placebo patients) from the study once the product becomes commercially available. To obviate the problems that would arise from the early drop-out of study patients, Genzyme had proposed converting AGAL-008 into an open-label, non-randomized study with comparison to an historical control. This approach was reviewed and discussed at the advisory committee and determined that it is not a valid analytic approach to this study. Further details regarding this proposed method and FDA review are contained in a separate FDA BLA review document.

To address the concern of loss of study participation, Genzyme has developed informational activity plans to work with investigators, patient advocacy groups, and study subjects that Genzyme believes will maximize the retention of patients in AGAL-008 even after the marketing approval is granted. Furthermore, Genzyme estimates that even if there is progressive drop-out of patients from the study over the several months following approval, it is likely that this will only modestly reduce the statistical power of the study, compared to the initial plan with completion in January 2004. This is due both to the over-enrollment of the study, and due to the advanced status of the study, where the remaining months of the study are only a relatively modest fraction of the entire study. Since statistical power calculations are only estimates of the potential for a study to provide a clear answer to the primary question, modest differences in estimated statistical power are unlikely to lead to major differences in the usefulness of the resulting study data.

In addition, Genzyme has agreed to obtain clinical data that may serve a supportive role in the goal of verifying the clinical benefit. Genzyme will monitor the participation in AGAL-008. If the number of placebo dropout patients is increasing to a degree that the data from the remaining randomized patients are providing little additional statistical power, then Genzyme will act to terminate the randomized-controlled design and offer all subjects in AGAL-008 open label agalsidase treatment with continued monthly monitoring for 18 months. In this manner Genzyme expects to have a number of subjects receiving placebo with monthly creatinine values for an extended period of time (perhaps 12 to 18 months) followed by monthly creatinine values for 18 months on agalsidase treatments. A within-patient analysis of the slope of creatinine over time, compared between the on-placebo and on-agalsidase periods may be able to offer supporting information regarding clinical efficacy. The power of this study will be limited, and cannot be calculated at this time as the exact number of AGAL-008 placebo patients that will be retained and eligible for enrollment into this pre-vs-post comparison study is unknown. Due to several aspects of this study, especially the non-randomized nature of this study, this study alone would be unable to constitute the adequate and well-controlled study to verify clinical benefit that is called for under the regulations. However, it is well suited to play a supportive role to the data from AGAL-008, in the event that the AGAL-008 are strongly suggestive, but not fully conclusive. This study and

analytic plan have not yet been submitted in detail to FDA, however the major features have been agreed upon; and this study will be a portion of the PMCs obtained from Genzyme.

In summary, Genzyme has proposed a comprehensive plan for obtaining data to verify that clinical benefit is associated with use of agalsidase beta. This plan rests primarily upon an adequate and well-controlled study. There is potential to supplement the evidence with data from a non-randomized, within-patient comparison study; but this will be only supportive. The major evidence will be from the adequate and well-controlled study AGAL-008. Genzyme has made plans which will attempt to minimize the impact of commercial availability upon the verification data from AGAL-008.

Recommendation

Genzyme has demonstrated an effect upon a surrogate endpoint that is reasonably likely to predict clinical benefit. Genzyme also appears to be acting with due diligence to verify the clinical benefit, primarily focusing on completing an ongoing (fully enrolled) study whose design will conform to being an adequate and well-controlled study. Marketing approval under the Accelerated Approval regulations does not appear likely to substantially impair Genzyme's ability to carryout their plan.

Therefore, Accelerated Approval can be recommended at this time for agalsidase beta for the treatment of Fabry disease.